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1: Arch Environ Health 2002 Sep-Oct;57(5):412-5

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High prevalence of anti-glutamic acid decarboxylase (anti-GAD) antibodies in employees at a polychlorinated biphenyl production factory.

Langer P, Tajtakova M, Guretzki HJ, Kocan A, Petrik J, Chovancova J, Drobna B, Jursa S, Pavuk M, Trnovec T, Sebokova E, Klimes I.

Institute of Experimental Endocrinology, Slovak Academy of Sciences, Bratislava, Slovakia. ueenlang@savba.savba.sk

An increased prevalence of thyroid antibodies was seen in employees of a factory that formerly produced polychlorinated biphenyls (PCBs). In this study, the authors expand the evaluation of possible long-term PCB effects by comparing the prevalence of glutamic acid decarboxylase (anti-GAD) antibodies with the development of diabetes mellitus. The sera of 240 factory employees and 704 control subjects were analyzed. Anti-GAD antibody values exceeded 1.20 U/ml in all employees (40.4%), was 4 times higher ($p < .001$) than in all controls (10.5%), and were 5 times higher in employees aged 51-60 yr (53.2%) than in age-matched controls (10.5%) ($p < .001$). Although the prevalence of diabetes could not be determined from this retrospective study, this is the first report of a possible relationship between xenobiotics and the prevalence of anti-GAD antibodies, and it supports the concept of an immunomodulatory effect of PCBs. However, such antibodies may be present decades before the development of clinical diabetes, and not all anti-GAD antibody-positive individuals become diabetic. Presently, it is unknown whether there is an increased prevalence of diabetes among the former factory employees.

PMID: 12641181 [PubMed - indexed for MEDLINE]

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☐ 1: Diabet Med 2002 Oct;19(10):832-5

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Metabolic and immunogenetic prediction of long-term insulin remission in African patients with atypical diabetes.

Sobngwi E, Vexiau P, Levy V, Lepage V, Mauvais-Jarvis F, Leblanc H, Mbanya JC, Gautier JF.

Department of Diabetes and Metabolic Diseases, and Clinical Investigation Centre, Saint-Louis Hospital, Paris, France.

AIMS: We aimed to characterize a cohort of 'atypical' diabetic patients of sub-Saharan African origin and to analyse possible determinants of long-term remission. METHODS: Over 6 years, we studied the clinical and therapeutic profile of 42 consecutive patients undiagnosed or untreated prior to inclusion presenting with cardinal features of diabetes mellitus. We measured insulin secretion and sensitivity at inclusion. Immunogenetic (anti-GAD, anti-ICA and HLA class II) markers of Type 1 diabetes were compared with a 90-non-diabetic unrelated adult African population. RESULTS: Twenty-one ketonuric patients (age 42 +/- 9 (sd) years; body mass index (BMI) 26 +/- 3 kg/m2) were initially insulin-treated (IT), and 21 non-ketonuric patients (age 38 +/- 8 years; BMI 26 +/- 5 kg/m2) had oral and/or diet therapy (NIT). Insulin could be discontinued in 47.6% (10/21) IT with adequate glycaemic control (HbA1c 6.7 +/- 1.3%), while insulin was secondarily started in 38.1% (8/21) NIT in expectation of better control. The initial basal (odds ratio (OR) 9.1, 95% confidence interval (CI) 1.3-64.4) and stimulated C-peptide (OR 8.17, 95% CI 1.5-44.1) were independently associated with remission. Insulin resistance was present in all the groups, more marked in the insulin-treated NIT. Anti-GAD antibodies and ICA were rare, but 38.1% IT vs. 1.1% controls had Type 1 diabetes HLA susceptibility haplotypes ($P < 0.001$) without significant difference between the subgroups. CONCLUSION: Prolonged discontinuation of insulin is frequent in African diabetic patients initially presenting with signs of insulinopenia. In our patients, long-term insulin therapy was not associated with immunogenetic markers of Type 1 diabetes. The initial measure of insulin secretion seemed a good predictor of long-term remission.

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☐ 1: Diabetes Care 1999 Dec;22(12):2049-54

Related Articles, Links

Progression to diabetes in relatives with islet autoantibodies. Is it inevitable?

Gardner SG, Gale EA, Williams AJ, Gillespie KM, Lawrence KE, Bottazzo GF, Bingley PJ.

Division of Medicine, University of Bristol, U.K.

OBJECTIVE: A large cohort of family members with islet cell antibodies (ICA) > or = 20 Juvenile Diabetes Foundation units (JDF U) was examined to determine whether there was a subgroup at low risk of progression to diabetes; whether risk of progression changed over time; and whether rate of progression to diabetes varied according to age, islet autoantibodies, and genetic markers of susceptibility. RESEARCH DESIGN AND METHODS: Individuals with ICA > or = 20 JDF U were identified from 4,423 family members recruited to prospective family studies in the U.K. Subjects were followed for up to 18 years. Antibodies to insulin, GAD, and IA-2 were measured in the first sample, and HLA class II typing was performed. RESULTS: Of 147 family members with ICA > or = 20 JDF U on at least one occasion, 29 developed type 1 diabetes after a median of 3.2 years (maximum 18.1). The cumulative risk of developing diabetes within 15 years was 47% (95% CI 28-67) for all family members with ICA > or = 20 JDF U, 2.8% (0-8.2) for those with ICA alone, and 66% (44-87) for those with at least one additional autoantibody marker. There were no differences in age, HLA class II type, or levels of ICA, insulin autoantibodies, or IA-2 antibodies between those who developed diabetes within 5 years of testing and those who developed diabetes after this time. GAD antibody levels we ..., however, higher in those who progressed more slowly. CONCLUSIONS: Family members with ICA alone are at low risk of progression to diabetes. Rapid development of disease after ICA detection could not be distinguished from delayed development on the basis of autoantibodies or markers of genetic susceptibility, and those with multiple antibodies remained at high risk throughout long-term follow-up. This suggests that all family members with multiple islet autoantibodies are destined to develop autoimmune diabetes.

PMID: 10587841 [PubMed - indexed for MEDLINE]

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1: Presse Med 1988 Dec 10;17(44):2340-3 Related Articles, Links

[Development of insulin reserves in the first 18 months in the insulin-dependent diabetic with or without remission of insulin-dependence]

[Article in French]

Brucker F, Boda-Buccino M, Bellet C, Fredenrich A, Fenichel P, Claude MH, Hieronimus S, Harter M.

Service d'Endocrinologie-Diabetologie-Nutrition et Medecine interne, Hopital de l'Archet, CHRU, Nice.

It seems rational to consider that residual insulin secretion is one of the factors which determine the short-term course of inaugural type I diabetes. But what about the mid-term course? We evaluated prospectively the insulin reserve (fasting and post-prandial C peptide) in 52 patients throughout the subsequent development of the disease. The patients (36 men, 16 women, mean age 35 years), who presented with ketonuria and weight loss, received a 10-day course of intensive insulin therapy, after which a remission of insulin dependence was observed in 40 of them (77 per cent). These 40 patients differed from those who had no such remission in that they were heavier and had a better initial insulin secretion. There was no significant difference between the two groups with regards to immunogenetic markers (presence of anti-islet antibodies 28/35 vs 8/12, DR3 and/or DR4 tissue group 27/37 vs 8/10). Following intensive insulin therapy, the C peptide value was consistently increased. At 6, 12 and 18 months the insulin secretion in patients of the remission group remained stable and always higher than that of patients who did not have a remission and whose insulin secretion collapsed at 18 months. Another characteristic of the remission group was that C peptide secretion could be stimulated by meals throughout the follow-up period (post-prandial C peptide at 18 months: 0.63 nmol/l). It is concluded that residual insulin secretion is one of the most effective predictive factors of remission when type I diabetes is first diagnosed and remains stable for the first 18 months of the disease in patients who show a remission.

PMID: 2974970 [PubMed - indexed for MEDLINE]

2: Diabete Metab 1990 Jul-Aug;16(4):303-10 Related Articles, Links

Probability of remission in individual in early adult insulin dependent diabetic patients. Results from the Cyclosporine Diabetes French Study Group.

Papoz L, Lenegre F, Hors J, Assan R, Vague P, Tchobroutsky G, Passa P, Charbonnel B, Mirouze J, Feutren G, et al.

INSERM Unite 21, Villejuif, France.

The aim of this study was to determine which candidates were suitable for immunotherapy among adult insulin dependent diabetic patients of recent onset. A statistical analysis was performed using the results of a multicentre randomized trial of cyclosporine versus placebo after nine months of treatment. When the baseline characteristics of the patients in remission were compared with those

not in remission, there was no difference observed either in initial residual beta-cell function (glucagon stimulated C-peptide level), or in immunological markers (T4 and T8 lymphocytes counts, Interleukin 2). The parameters showing the most difference were, in addition to treatment group, the duration of diabetes symptoms and body mass index at inclusion, and the HLA-DR phenotype. This was confirmed using a logistic regression analysis, in which these variables were found to be significantly related to remission. The probability of remission in each individual patient was then calculated using these variables in the mathematical function provided by the logistic model. Ninety eight out of 110 patients were correctly classified using this method. In addition, it must be noted that only subjects adequately treated by cyclosporine were still in complete remission after a one year follow-up. Conversely, it appeared that immunosuppression in subjects having a predicted probability of remission lower than 0.35 using the mathematical function, and being non-DR3, non-DR4 has to be avoided. These results will be useful in optimizing the recruitment of patients in on-going or future trials of immunotherapy in early diabetes.

Publication Types:
- Clinical Trial
- Multicenter Study

PMID: 2265735 [PubMed - indexed for MEDLINE]

☐ **3:** Diabetologia 1990 Sep;33(9):561-8 Related Articles, Links

Islet cell antibodies and fasting C-peptide predict insulin requirement at diagnosis of diabetes mellitus.

Landin-Olsson M, Nilsson KO, Lernmark A, Sundkvist G.

Department of Medicine, Malmo General Hospital, University of Lund, Sweden.

The differential diagnosis between Type 1 (insulin-dependent) and Type 2 (non-insulin-dependent) diabetes is complicated since no specific markers are available for either disease. In this study, 244 consecutive patients were diagnosed with diabetes mellitus during two years in Malmo (230,000 inhabitants), corresponding to an incidence rate of 53.100,000(-1).year-1. Age, body mass index, HbA1c, C-peptide, and levels of islet cell antibodies were determined at the clinical onset, and related to the classification at diagnosis and at follow-up (n = 233) after a median time of 31 (range 1-49) months. After diagnosis, 42 of 244 (17%) were started on insulin while 202 of 244 (83%) were not. Islet cell antibodies were present in 25 of 42 (60%), and in 18 of 183 (10%), respectively. In the non-insulin treated group, patients with islet cell antibodies had lower body mass index (p less than 0.001), higher HbA1c (p less than 0.004), and lower C-peptide (p less than 0.001) than patients without. At follow-up, 11 of 18 (61%) islet cell positive patients were changed to insulin treatment, as were six other patients. Insulin was discontinued in five initially insulin-treated but islet cell antibody negative patients. The sensitivity, specificity and predictive value for insulin treatment at follow-up were for islet cell antibody positivity; 72%, 96% and 84%, respectively, and for low C-peptide value; 60%, 96%, and 80%, respectively. Islet cell antibodies and low C-peptide at diagnosis of diabetes mellitus are concluded to be useful markers to predict insulin dependence.

PMID: 2253834 [PubMed - indexed for MEDLINE]

☐ **4:** Diabetes Res Clin Pract 1993 Feb;19(2):151-62 Related Articles, Links

Immunoprotection in spontaneous remission of type 1 diabetes: long-term follow-up results.

Yilmaz MT, Devrim AS, Biyal F, Satman I, Arioglu E, Dinccag N, Karsidag K, Ozden I, Gurel N, Sipahioglu F, et al.

Department of Internal Medicine, Istanbul Faculty of Medicine, Istanbul University, Turkey.

This prospective pilot study was undertaken to test the efficacy of oral methyl-prednisolone (MP) therapy at spontaneous remission phase of type 1 diabetes in intervening the course of the disease. Twenty-five type 1 diabetic patients who were classified as having a spontaneous remission (honeymoon) were divided into treatment and non-treatment groups on voluntary basis. Fifteen patients thus making up the treatment group (13 males and 2 females, mean age 23.8 +/- 6.2 years) received 0.7-1.0 mg/kg/day of MP p.o. for 2 weeks. The dose of the drug was then gradually diminished every week until 5 mg/day (approx. 0.1 mg/kg/day) and discontinued at 10 +/- 2 weeks. In case of hyperglycemia occurring in 12 of 15 patients due to the administration of steroid, insulin was used to normalize blood glucose levels (average 0.47 +/- 0.21 IU/kg/day). The non-treatment group (8 males and 2 females, mean age 21.8 +/- 8.9) did not receive any special medication or placebo except for insulin whenever necessary to regulate glycemia. Upon completion of protocol, all patients in treatment group displayed clinical remission with 10 still in non-insulin requiring remission for follow-up periods ranging between 16 and 91 months. The remaining 5 patients relapsed within 3-15 months of therapy. Other metabolic (including basal and stimulated C-peptide levels) and immunological indices that have spontaneously ameliorated with the occurrence of honeymoon were also maintained within normal range in the NIR patients. Meanwhile, natural remission in the non-MP-treated group terminated at 3.4 +/- 0.6 months with deterioration of all metabolic and immunological markers as well as increasing requirements for insulin. In conclusion, the spontaneous remission of the patients could be prolonged significantly by MP therapy as opposed to no therapy ($P < 0.001$). These results suggest that the spontaneous remission phase may be a crucial point of intervention in immunotherapy of type 1 diabetes and that randomized trials with MP at this particular phase would be worthwhile.

Publication Types:
- Clinical Trial

PMID: 8472630 [PubMed - indexed for MEDLINE]